Radiotherapy for metastatic fibrolamellar hepatocellular carcinoma

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Abstract

Fibrolamellar hepatocellular carcinoma (FLHCC) is a rare variant of hepatocellular carcinoma (HCC) that commonly affects young individuals without a prior history of liver disease. FLHCC commonly results in a better prognosis than HCC; however, the risk of recurrence and metastatic disease is high. FLHCC is typically treated by primary resection of the tumor with 50-75% cure rates. The use of radiation therapy in FLHCC has not been assessed on its own, and may show some success in a very few reported combination therapy cases. We report on the successful use of radiation therapy in a case of metastatic FLHCC to the lung following primary and secondary resections. Our treatment of the large, metastatic, pulmonary FLHCC tumor with 40 Gy in 10 fractions resulted in an 85.9% tumor volume decrease over six months. This suggests FLHCC may be a radiosensitive tumor and radiotherapy may be valuable in unresectable or metastatic tumors.

Introduction

Fibrolamellar hepatocellular carcinoma (FLHCC), a rare variant of hepatocellular carcinoma (HCC) comprising 1-2% of the US HCC cases. FLHCC was first described by Edmondson in 1956;[1,2] it histologically consists of polygonal, eosinophilic hepatocyte cords separated by bands of fibrous stroma.[1,3] FLHCC tumors typically present with symptoms of abdominal pain, fullness, and nausea.[1,3] Unlike HCC, FLHCC commonly affects young individuals (mean age of 25 years) with no previous history of liver disease.[1,3] FLHCC tumors are also generally larger on presentation, have lower alpha-fetoprotein (AFP) values, and have a more favorable prognosis.[1,3] Despite the high surgical resection cure rate (50-75%), FLHCC has a high recurrence and distant metastasis rates of nearly 50% requiring additional resection, liver transplantation, chemotherapy, or radiation therapy.[1,4] Little evidence exists to indicate whether FLHCC responds well to traditional chemotherapy or radiation therapy.[4-6] We present the case of a patient with FLHCC lung metastases which were successfully treated with radiation treatment.

Case Report

A 28-year-old Caucasian female presented to her local urgent care center with flu-like symptoms and fatigue. On physical exam, an abdominal mass was palpated, prompting a computed tomography (CT) scan of her abdomen. A large, heterogenous enhancing mass with central low attenuation change was discovered in the left liver lobe. She later indicated that she had felt abdominal fullness and pain in the left upper quadrant, but denied constitutional symptoms, jaundice, or pruritis. The patient had a significant family history for ovarian, lung, prostate, and breast cancer. She had a 10 year history of smoking one pack per week. Testing for Hepatitis B and C were both negative. The patient's presenting lab values included AFP 7.8 ng/mL, alkaline phosphatase 115, AST 72, ALT 124, total/direct bilirubin 0.9/0.2, Na 139, K 4.2, Platelets 400, and INR 1.0. Biopsy of the mass confirmed a grade 1-2 FLHCC and chest imaging did not reveal any metastases.

The patient underwent a left lateral liver resection to remove the 11.7×9.8×6.1 cm FLHCC mass. The surgical margins were negative with no evidence of vascular invasion; however, three out of six hepatic artery and periportal lymph nodes were positive for FLHCC. Following resection, the patient did not receive chemotherapy. Three months after the operation, her AFP levels had declined to <0.8 ng/mL and imaging was negative for metastatic disease. During the seventeen months following the liver resection, the patient had two separate surgical interventions to remove growing abdominal and thoracic lymph nodes and masses. At twenty-two months following the liver resection, the patient noted a cough and was found to have a new, large (2.6×2.3 cm), right hilar lymph node as well as old and new pulmonary nodules. At this time, radiation oncology was consulted to treat the right hilar lymph node. She was not deemed a suitable candidate for definitive radiation treatment at that time, due to the numerous enlarging areas of metastatic disease and the lack of symptoms from the hilar metastasis. After three months of watching, the right hilar node decreased in size, but multiple subpleural and subcarinal nodules arose, and a perigastric lymph node continued to grow slightly. The patient decided to not pursue treatment at that time and decided to watch and wait. Three months later CT imaging showed significant growth of the subpleural nodules and right hilar nodules with maintenance of the subcarinal lymph nodes. The patient continued to decline standard treatments.

Four months later, the pulmonary nodules had grown significantly large (one measured 6×10 cm) as well as a lymph node on the gastrohepatic ligament (Figure 1). The patient began to have symptoms of a dry cough and shortness of breath due to mass effect and invasion of the chest wall. At this time, we began palliative radiation treatment of the pulmonary metastasis with 40 Gy in ten fractions over a thirteen day time period (Figure 1). The patient tolerated the radiation therapy well and began capecitabine and interferon alfa-2b therapy eight days after the radiation treatment. She developed symptoms consistent with radiation pneumonitis approximately 85 days after treatment, which resolved with prednisone.

The FLHCC pulmonary metastases showed a remarkable response to the radiation treatment. We utilized Eclipse software to contour and record dimensions and volumes for the treated metastatic tumor. According to the RECIST criteria, the patient was classified as a partial response.[7] Measurements of the treated metastatic right lung mass pre-treatment resulted in a maximal left-right (LR) diameter

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of 9.1 cm, a maximal anterior-posterior (AP) diameter of 10.6 cm, a maximal superior-inferior (SI) diameter of 14.0 cm, and a volume of 538 cm^3 (Figure 1). At four months post-treatment, the mass measured LR diameter 7.6 cm, AP diameter 5.6 cm, SI diameter 9.1 cm, and volume 100 cm^3 (Figure 2), and at six months post-treatment, the mass measured LR diameter 7.6 cm, AP diameter 5.8 cm, SI diameter 8.5 cm, and volume 75.8 cm^3 (Figure 3). These changes constitute a 81.4% and 85.9% decrease in tumor volume and a 35.0% and 39.3% decrease in the longest diameter (SI diameter) at four and six months respectively. The effect was exclusive to the treated pulmonary metastases treated with radiation. Other known metastatic lesions progressed during the chemotherapy suggesting the response was due primarily to the radiotherapy. Unfortunately the patient continued to develop pulmonary metastases (Figures 2 and 3). Due to the prior pneumonitis, radiotherapy had been held and chemotherapy was used to treat the progressive disease. The response in the treated metastases had been durable during the 6 months of follow-up (Figures 2 and 3).

Discussion and Conclusions

We report here on an excellent clinical and radiographic response to pulmonary FLHCC metastases treated with radiotherapy. There have been very few reports of FLHCC treated with radiation therapy.[4-6] In these studies, radiation therapy has been used to treat unresectable primary tumors,[5] to convert unresectable to resectable tumors,[6] and to treat metastases or relapses.[4] The radiation therapy in these studies was commonly combined with chemotherapy as an aggressive treatment and not separately analyzed. Many patients receiving these aggressive treatments showed a positive response to the treatment, leading to tumor resectability or increased overall survival.[4-6] Despite these reports, there is doubt in the literature regarding the effectiveness of radiotherapy in FLHCC.[3,8,9] We utilized radiation therapy in this patient primarily as a means of palliation for worsening respiratory symptoms. However, we can imagine that radiation therapy may be used as an aggressive combination therapy together with surgery and chemotherapy. Our successful experience with radiation treatment of FLHCC metastasis to the lung together with reported combination therapy in the literature suggests that radiation treatment of primary or metastatic FLHCC may provide an effective means of targeting the primary disease, preventing recurrences, and treating metastases or relapses. We report this case as an example of FLHCC showing response to radiation treatment. Further research into the role of radiotherapy for FLHCC is warranted.

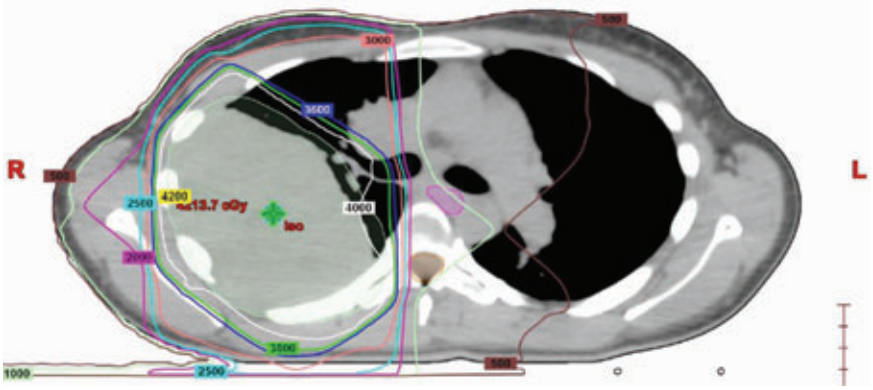

Figure 1. Radiation treatment plan for metastatic pulmonary tumor. Isodose lines reflect predicted radiation delivered to tumor and surrounding tissues.

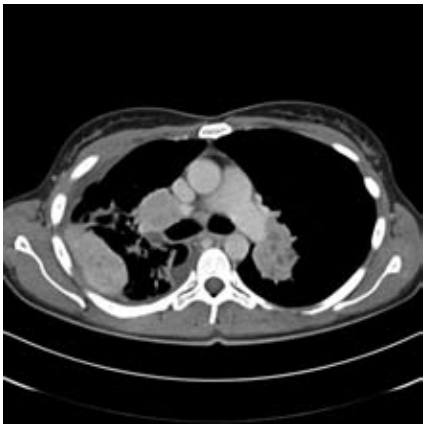

Figure 2. Four month post-radiotherapy computed tomography scan of pulmonary metastatic fibrolamellar hepatocellular carcinoma tumor.

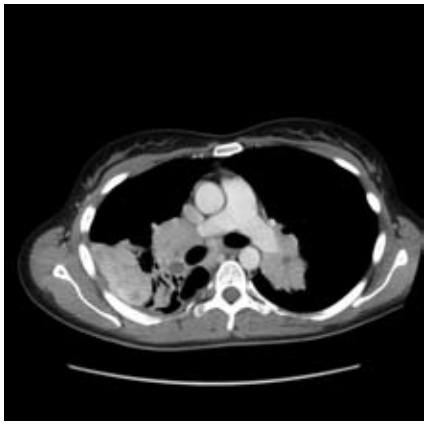

Figure 3. Six month post-radiotherapy computed tomography scan of pulmonary metastatic fibrolamellar hepatocellular carcinoma tumor.

References

1. Liu S, Chan KW, Wang B, Qiao L. Fibrolamellar hepatocellular carcinoma. Am J Gastroenterol 2009;104:2617-24.
2. Edmondson HA. Differential diagnosis of tumors and tumor-like lesions of liver in infancy and childhood. AMA J Dis Child 1956;91:168-86.
3. Ward SC, Waxman S. Fibrolamellar carcinoma: a review with focus on genetics and comparison to other malignant primary liver tumors. Semin Liver Dis 2011;31:61-70.
4. Maniaci V, Davidson BR, Rolles K, et al. Fibrolamellar hepatocellular carcinoma: prolonged survival with multimodality therapy. Eur J Surg Oncol 2009;35:617-21.
5. Epstein BE, Pajak TF, Haulk TL, et al. Metastatic nonresectable fibrolamellar hepatoma: prognostic features and natural history. Am J Clin Oncol 1999;22:22-8.
6. Sitzmann JV. Conversion of unresectable to resectable liver cancer: an approach and follow-up study. World J Surg 1995;19:790-4.
7. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
8. Li W, Tan D, Zenali MJ, Brown RE. Constitutive activation of nuclear factor-kappa B (NF-kB) signaling pathway in fibrolamellar hepatocellular carcinoma. Int J Clin Exp Pathol 2010;3:238-43.
9. Farmer DG, Rosove MH, Shaked A, Busuttil RW. Current treatment modalities for hepatocellular carcinoma. Ann Surg 1994; 219:236-47.